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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/582,246	HAGEN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *3,7 and 9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 21 September 2000 as the U.S. national stage of international application PCT/EP98/08216. The preliminary amendment filed 22 June 2000 has been entered. Claims 1-13 are pending.

Election/Restrictions

Applicant's election of Group I (claims 1-6, 8 and 13) in the Paper filed 30 October 2003 is acknowledged. Because applicant did not distinctly and specifically point out errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In an interview with Applicant's representative, the examiner clarified that, to the extent that the claims are directed to a specific sequence, the elected group is restricted to examination of SEQ ID NO: 4. Applicant's representative acknowledged their election of SEQ ID NO: 4 for examination.

Claims 3, 7 and 9-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention. Claims 1, 2, 4-6, 8 and 13 are presently under consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2 and 8 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1 and 2, as written, do not sufficiently distinguish over nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring properties of the claimed products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Claim 8 is directed to recombinant host cells harboring the recombinant nucleic acids of the claims. As the specification contemplates transgenic animals comprising the nucleic acids (e.g., page 11, lines 1-2) and does not exclude human beings from the scope of transgenic animals, the broadest reasonable interpretation of claim 8 includes recombinant host cells of a transgenic human, which is nonstatutory subject matter. Amending the claim to recite, for example, "Recombinant host cells in culture" would overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: Claim 13 is directed to a medicament comprising a vector comprising a regulatory DNA sequence for the gene for the human catalytic telomerase subunit. As the claim is specifically directed to medicament, it is understood that the intended use for the composition is as a therapeutic and the enabling disclosure must therefore teach the skilled artisan how to use the composition therapeutically. Further, with respect to therapeutic application of the regulatory sequences disclosed in the application, the specification contemplates only gene therapy (e.g., at page 10) and gene therapy of cancer in particular (see, e.g., the discussion beginning at page 6, line 29 through page 8, line 2). Therefore, the disclosure must teach the skilled artisan how to use the claimed compositions for gene therapy.

State and level of predictability in the art: At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (e.g. adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA

vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

In an article published well after the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remain

unsolved long after the application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. Several teachings from the relevant art indicate that, at the time of filing, realizing treatment of any cancer using the methods set forth in the instant disclosure would require undue experimentation. First, with regard to general enablement for treatment of cancer using a gene therapy approach, the post filing art clearly indicates that the cancer gene therapy remains in an early stage of development with many obstacles remaining to be overcome before effective therapy becomes routine. Gomez-Navarro *et al.* (2002) From: *Mol. Basis Hum. Cancer* (W.B. Coleman and G.J. Tsongalis, eds.), Humana Press Inc., Totowa, NJ, pages 541-556 teaches "[t]o accomplish any gene therapy approach, certain basic criteria must be met to allow an effective genetic intervention. In this regard, gene-therapy approaches are based on the fundamental ability to deliver therapeutic nucleic acids into the relevant target cells. Further, the delivered genes must be expressed at an appropriate level and for an adequately prolonged period of time" (page 542, first full paragraph). Gomez-Navarro *et al.* goes on to teach, "[a]lthough many potentially effective strategies exist to effect the molecular treatment of cancer, gene-delivery

issues currently limit the definitive evaluation of these methods" (page 542, paragraph bridging columns 1 and 2). Thus, Gomez-Navarro *et al.* clearly teaches that cancer gene therapy is subject to the constraints outlined above that have generally hindered progress in gene therapy.

Gomez-Navarro *et al.* also teach that, even success in treating experimental animal models has not been translated into success in the clinic. In the paragraph bridging columns 1 and 2 on page 550, Gomez-Navarro *et al.* teaches, "[t]herapies based on gene transfer have been shown to be remarkably successful in vitro and in vivo animal model systems. However, overriding limitations have consistently been made apparent in pre-clinical experiments and in the first human gene –therapy clinical trials." Thus, well after the filing date of the instant application, successful gene therapy was not enabled even for those treatments that had demonstrated success in animal model systems.

Gomez-Navarro *et al.* indicate that *in situ* therapies are particularly problematic. In the second column on page 551, Gomez-Navarro *et al.* teaches that efficiencies of presently available vectors are inadequate to achieve effective level of transduction, "[e]ven in closed-compartment delivery contexts, it has not been possible to modify a sufficient number of tumor cells to achieve a relevant tumoral response in clinical models" (final paragraph on page 551). Hermann *et al.* (1995) *J. Mol. Med.* 73:157-163 concurs, stating, "[m]ajor obstacles for gene transfer arise from the low transfection efficacy (maximum of 10% of target cells for retroviral vectors) and the lack of target specificity. Both problems require the use of an ex vivo/in vitro approach. For any in vivo application, either systemically or locally, the vector used must be able to target a particular cell in a specific way" (paragraph bridging pages 158 and 159). In the

instant case, neither the specification nor the art teach how to effectively target the claimed compositions.

Gomez-Navarro *et al.* concludes, "major problems remain to be solved before [approaches to intervention at the molecular level for therapeutic purposes] can become effective and commonplace strategies for cancer. Principle among these is the basic ability to deliver therapeutic genes quantitatively, and specifically, not only into tumor cells but also into tumor supporting tissues and effector cells of the immune system" (final paragraph on page 559). Thus, Gomez-Navarro *et al.* teach that achieving a therapeutic effect using technologies available in the art well after the filing date of the instant application was far from predictable or routine.

Amount of direction provided by the inventor and existence of working examples: The teachings of the instant specification are primarily focused on isolation of the human catalytic telomerase subunit gene and characterization of regulatory regions within the gene. Although portions of the region 5' to the transcriptional start site were identified as capable of providing expression of a reporter gene in cultured cell lines, the specification provides no specific guidance as to how these nucleic acids might be used therapeutically. In particular, none of the teachings provided in the specification address the problems encountered in attempts to establish an effective gene transfer vehicle. Furthermore, there is no evidence provided to indicate that the disclosed promoter would be capable of providing transgene expression at a therapeutic level and duration. Thus, the instant disclosure provides essentially no guidance that would enable the skilled artisan to overcome the myriad of problems that would be encountered by the skilled artisan seeking to use the claimed medicament at the time of filing.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the medicament of the instant claim without first engaging in undue experimentation. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. Given the many factors affecting gene transfer and expression *in vivo* and the absence of existing working examples the level of experimentation required is clearly beyond what is considered routine in the art. Therefore, the teachings of the specification and prior art would not enable the ordinary skilled artisan to use the invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-6, 8 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in being directed to regulatory DNA sequences <u>for</u> the gene for the human catalytic telomerase subunit. Although it seems that applicant intends to claim regulatory DNA sequences isolated from the native human catalytic telomerase subunit gene, the claim can also be understood as reading on any regulatory DNA sequence that can be used <u>for</u> expressing

the the human catalytic telomerase (e.g., a viral promoter sequence). It is therefore unclear exactly what is being claimed. Amending the claim such that it is directed to regulatory sequences isolated from the human catalytic telomerase subunit would overcome this rejection. Claims 2, 4-6, 8 and 13 are indefinite insofar as they depend from claim 1.

Claim 2 is additionally indefinite in reciting "intron sequences in accordance with" the various disclosed sequences. It is unclear whether the claimed nucleic acids must comprise the disclosed sequences or whether they might be in accordance with the disclosed sequences in some other way. Amending the claim to describe the subject matter using language such as "comprising" or "consisting of" the disclosed sequences is recommended.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4-6 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Cech *et al.* U.S. Patent No. 6,475,789 (filed 14 August 1997).

Cech *et al.* discloses the nucleic acid sequence of the human telomerase catalytic subunit gene, including the region immediately 5' to the transcriptional start site (i.e., SEQ ID NO: 6) and the sequence of the first intron (i.e., SEQ ID NO: 7). SEQ ID NO: 6 and 7 of Cech *et al.* anticipate the regulatory DNA sequences of the instant claim 1, and SEQ ID NO: 7 of Cech *et al.* anticipates SEQ ID NO: 4 of claim 2 (i.e., comprises a sequence 100% identical to SEQ ID NO: 4).

Throughout the specification, Cech *et al.* contemplates a variety of recombinant constructs comprising the isolated telomerase catalytic subunit (hTRT) gene regulatory elements according to claim 4, including a vector containing DNA sequences encoding polypeptides according to claims 5 and 6 which is further comprised within a host cell according to claim 8 (see especially column 17, lines 45-51 and Example 14).

Cech *et al.* teaches nucleic acids and cells comprising all of the limitations of the instant claims; thus, the claims are anticipated by Cech *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

DAVID GUZO
PRIMARY EXAMINER